UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

In re: EPHEDRA PRODUCTS LIABILITY LITIGATION	04 MD 1598 (JSR)
	OPINION AND ORDER

PERTAINS TO ALL CASES

JED S. RAKOFF, U.S.D.J.

In Case Management Order No. 14 dated June 23, 2005, the Court granted in part and denied in part the respective motions of the Defendants' Coordinating Counsel (the "DCC") and Plaintiffs' Coordinating Counsel (the "PCC") to exclude, pursuant to Rule 702, Fed. R. Evid., and *Daubert v. Merrell Dow Pharm.*, 509 U.S. 579 (1993), the testimony of certain "generic" experts. Specifically, the Court held that

> [t]he PCC's experts shall not be permitted to testify with "medical certainty" or "scientific certainty" that ephedra caused the alleged injuries. However, they will be permitted to testify (if otherwise admissible under applicable state and federal law) that ephedra may be a contributing cause of stroke, cardiac injury, and seizure in some people. A Memorandum Order [or, as here, an Opinion and Order] further detailing and elaborating on these ruling and including other holdings, such as more particularized rulings on the opinions offered by Dr. James Knochel and Dr. Kristie L. Ebi, will be filed in due course.

Case Management Order No. 14, June 23, 2005, ¶ 3. As promised, this Opinion and Order serves to explain, elaborate, and refine those determinations and decide certain related, outstanding

issues.

By way of background, there are presently consolidated before the Court about 500 civil actions claiming personal injury or wrongful death caused by dietary supplements containing ephedra. Some 360 were transferred here pursuant to 28 U.S.C. § 1407 for pretrial purposes only, while the remainder -- cases against the former Twin Laboratories Inc., a debtor in bankruptcy in this district, plus a few other cases commenced in this district -- are here for all purposes. Following consolidation, the Court issued Case Management Order No. 1, dated April 26, 2004, which among other things, provided that the PCC

> shall identify, in a document served on all parties, generic expert witnesses who are reasonably expected to testify [at subsequent trials] for the plaintiffs on issues of general or widespread applicability ("Generic Experts"), including, but not limited to, experts who will testify on general causation. The plaintiffs may identify up to three Generic Experts with respect to each of the following categories of injuries: (a) ischemic stroke, (b) hemorrhagic stroke, (c) seizures, (d) cardiac injury, (e) psychotic injury, and (f) primary pulmonary hypertension. For each Generic Expert so identified, Plaintiffs' Coordinating Counsel, on behalf of all plaintiffs, shall serve upon all parties the disclosures required by Fed. R. Civ. P. 26(a)(2), except that such disclosures need not include such testimony, if any, that such Generic Expert is expected to offer relating only to liability or damages as to a particular plaintiff.

Case Management Order No. 1, April 26, 2006, at 22-23. Further, the Order permitted the DCC to designate responsive generic

experts and directed the PCC and DCC to complete generic-expert depositions and make any Rule 702 motions by specified dates. By subsequent agreements approved by the Court, heat-related injury was added as a topic for generic experts, while psychotic injury and pulmonary tension were removed from the generic expert category and made the responsibility of counsel in individual cases.

In compliance with the foregoing, the DCC moved in December 2004 to exclude the testimony of all nine generic experts designated by the PCC, while the PCC moved to exclude the testimony of one of the DCC's designated experts. In January and February 2005, the Court held an extensive "*Daubert*" hearing, at which all ten challenged experts testified and were cross-examined, along with two other experts called by the DCC in support of their motion. In addition, hundreds of documents -- mainly articles from medical journals and textbooks -- were received as exhibits at the hearings. (They will be referred to hereafter as "PCC Exh. __" and "DCC Exh. __".) The parties then submitted post-hearing briefs and made their closing oral arguments on March 16, 2005.

Ephedra is plant, also known by the Chinese name ma huang, that contains several chemically related biologically active

substances known as "ephedrine alkaloids."[1] The ephedra products in these cases combined ephedra with caffeine and were marketed to consumers seeking weight loss, increased energy and improved athletic performance. The predominant ephedrine alkaloid in all the products was ephedrine itself, which is chemically identical to the synthetic ephedrine contained in some pharmaceutical products. Since ephedrine accounts for more than 70% of the ephedrine alkaloids in ephedra, and since the others have similar (though not identical) biological effects, the parties, experts and scientific literature often use data on synthetic ephedrine as a surrogate for data on the mix of ephedrine alkaloids found in ephedra products. The label of Metabolife 356 (the most widely distributed product involved in the pending cases) states a "suggested use" of one or two capsules every four hours with a maximum of eight capsules per day, which adds up to 96 mg per day of ephedrine alkaloids. PCC Exh. 16.

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[1] *See* Middleton WS and Chen KK, *Ephedrine, A Clinical Study* (ARCH. INTERN. MED., 1927, 39:385-403), DCC Exh. A386. According to the authors, ephedrine was first isolated from herbal ephedra in 1887, and synthetic ephedrine was first patented in 1918. In their clinical study begun in 1924, the authors administered various doses of ephedrine to 41 volunteers “in order to determine the effects of ephedrine given internally.” *Id.* at 387. Case 24, a woman with prior heart disease, “died twenty hours following the administration of the drug.” *Id.* at 393. The authors state in their Conclusions: "The drug should not be used without extreme caution in cases of cardiovascular diseases or markedly deficient circulation." *Id*. at 403. Their conclusions also report that ephedrine when given by mouth caused a rise in blood pressure lasting an average of five hours and nine minutes. *Id*. at 402.

The main issue presented by the DCC's motion to exclude the PCC's generic experts is whether there may be introduced into evidence, consistent with the requirements of Rule 702, testimony that ephedra causes strokes, heart attacks, and heat stroke (the "listed injuries"). This is often referred to as an issue of "general causation" (*i.e.*, does use of ephedra cause a given kind of injury), as opposed to specific causation (*i.e.*, did a given person's use of ephedra cause his particular injury). While many federal cases state that a plaintiff, in order to recover in a "toxic tort" case, must prove both general and specific causation, *see, e.g., In re Rezulin Products Liability Litigation*, 369 F. Supp. 2d 398, 401-02 & n.9 (S.D.N.Y. 2005) (collecting cases), in the cases here consolidated what plaintiffs must prove is determined by state law. Neither side here, however, has suggested that general causation is not a requirement under the law of the relevant states, and the Court will so assume for purposes of this motion.

Assuming, then, that general causation is part of what any plaintiff here must prove in order to ultimately prevail, expert testimony about general causation is sufficiently reliable to be admissible under Rule 702 if "(1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case."

Rule 702, Fed. R. Evid.

In contending that the PCC's generic experts fail to meet these requirements, the DCC's primary argument is as follows: The parties agree that any listed injury caused by ephedra would manifest itself within a relatively short time after ingestion. Tens of thousands of people have used ephedra products at recommended doses without manifesting a listed injury, and millions of people have suffered the listed injuries without using ephedra. Where a listed injury has occurred, there is no post-injury examination or autopsy that can determine whether the injury was caused by ephedra. Under these circumstances, the only scientifically valid way to prove general causation is by controlled epidemiological studies with statistically significant results showing that ephedra (or ephedrine) materially increases the risk of the listed injuries. Since there are no such studies yielding such results, the PCC's experts should be excluded because their opinion that ephedra causes the listed injuries is not scientifically valid and therefore not reliable under Rule 702.

This argument finds superficial support in certain dictum in *Daubert*, where the Supreme Court stated that "[i]n a case involving scientific evidence, *evidentiary reliability* will be based upon *scientific validity*." *Id.* at 591 n.9 (emphasis in original). Nevertheless, for reasons developed below, the Court

is persuaded by the DCC's view of science but not by its interpretation of the law. The evidentiary hearings demonstrated that general causation has not been established by scientific standards of proof. Accordingly, the PCC's witnesses will not be permitted to testify with any degree of medical or scientific "certainty" that ephedra causes the listed injuries. However, the absence of epidemiological studies establishing an increased risk from ephedra of sufficient statistical significance to meet scientific standards of causality does not mean that the causality opinions of the PCC's experts must be excluded entirely. The hearings also demonstrated that the PCC's experts have a reliable basis for forming a professional opinion that ephedra may be a contributing cause of cardiac injury and stroke in some people, such as those with a heart condition, high blood pressure, or a genetic sensitivity to ephedrine, if that opinion is appropriately qualified. Accordingly, the PCC's experts will be permitted to express that opinion (if relevant) at trial, provided that they qualify it with a statement that there is not enough data to prove it definitively and that controlled studies, if and when they are done, may disprove it.[2]

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[2]Such subsequent disproof of medical opinions once widely held is relatively rare but from far from unprecedented. Thus, for example, digitalis, which accepted medical doctrine once held beneficial to heart failure patients, was later shown by controlled studies to be ineffective, and beta blockers, which medical doctrine once thought harmful to heart patients, were later shown by controlled studies to be beneficial. A recent,

Turning first to the legal standard: although, as noted, there is dictum in *Daubert* that could be read to support the DCC's position, it must be read in light of the subsequent development of the law. After *Daubert*, the Supreme Court decided two more Rule 702 cases,[3] and then promulgated an amendment to Rule 702 that took into account not only the three Supreme Court opinions but also many post-*Daubert* decisions of the lower courts. *See* Rule 702, Committee Notes on Rules, 2000 Amendment.

Even prior to the amendment to Rule 702, two Second Circuit holdings had rejected the argument that *Daubert* requires exclusion of a causation opinion unless it is based on published studies. *Zuchowicz v. United States,* 140 F.3d 381, 386-87 (2d Cir. 1998); *McCullock v. H.B. Fuller Co.,* 61 F.3d 1038, 1043-44 (2d Cir. 1995). After the amendment to Rule 702, a third Second Circuit decision, *Amorgianos v. National Railroad Passenger Corp*., 303 F.3d 256 (2d Cir. 2002), signaled the continuing authority of *Zuchowicz* and *McCullock* under the amended Rule by repeatedly citing and relying on them. *Id.* at 265-67.

Zuchowicz and *McCullock* stand for the proposition that "differential etiology" properly performed by a qualified

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well publicized example is estrogen replacement in menopausal women -- for many years a generally accepted treatment -- which controlled studies have now shown to be detrimental in many instances.

[3]*Kumho Tire Co. v. Carmichael,* 526 U.S. 137 (1999); *General Electric Co. v. Joiner,* 522 U.S. 136 (1997).

physician is sufficiently reliable to render admissible the physician's opinion on causation. *McCullock* describes differential etiology as a "scientific analysis" which "requires listing possible causes, then eliminating all causes but one." 61 F.3d at 1044. It is a method of legal proof approved by the Second Circuit for showing the external cause (*e.g.*, ephedra) of an injury. Some other courts call this method of proof "differential diagnosis," borrowing from medicine the name of a technique used to identify the disease or disorder causing observed symptoms, for the purpose of treatment and prognosis. *See* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE (Federal Judicial Center, 2d ed. 2000) at 443-444. What differential diagnosis in medicine and differential etiology in law have in common is the use of medical knowledge, training and experience to list and eliminate possible causes. The legal analysis in individual cases often does not separate general and specific causation as has been necessary here in order to decide together issues of general causation that are common to dozens of MDL cases. Nevertheless, the experts in *Zuchowicz* and *McCullock*, when they listed the possible causes, were stating an opinion on general causation.

In *McCullock*, in particular, the court affirmed admission of a physician's causation opinion even though he "could not point to a single piece of medical literature that says glue fumes cause throat polyps." 61 F.3d at 1043. Here, in contrast, the

PCC's experts cite a considerable amount of medical literature supportive of their view -- just none reporting controlled epidemiological studies with statistically significant results showing general causation. Any rule that would automatically exclude causation testimony unless it is based on such studies is irreconcilable with *Zuchowicz* and *McCullock* and with the admonition in *Amorgianos* that "[s]uch a bright-line requirement would be at odds with the liberal admissibility standards of the federal rules and the express teachings of *Daubert"* about the need for flexibility in the district court's gate-keeping role. 303 F.3d at 267.

Under Rule 702, federal courts routinely permit witnesses with "technical or other specialized knowledge" to state opinions on matters where the data falls short of proving the witness's conclusion. For example, an art appraiser testifying about a painting's authenticity might state an opinion based in part on scientific analysis, but the ultimate conclusion would come from the witness's specialized knowledge, training and experience. Scientists, too, form professional opinions that are reasonably based on "good science" but where the data is insufficient for definitive scientific proof. To hold the opinions of scientists inadmissible unless backed by statistically significant results from tightly controlled (and very expensive) experiments would set a separate, higher standard for scientists than for other

witnesses with specialized knowledge.

Such a difference is without support in the language of Rule 702 itself, which "makes no relevant distinction between 'scientific' knowledge and 'technical' or 'other specialized' knowledge." Moreover, there is no "convincing need to make such distinctions. Experts of all kinds tie observations to conclusions through the use of what Judge Learned Hand called 'general truths derived from ... specialized experience.'" *Kumho Tire,* 526 U.S. at 148, quoting L. Hand, *Historical and Practical Considerations Regarding Expert Testimony*, 15 Harv. L. Rev. 40, 54 (1901). The Court in *Kumho Tire* rejected the view that Rule 702 sets a *lower* standard for witnesses with "technical or other specialized knowledge" than for scientists. But its reasoning cuts both ways: if art appraisers, handwriting experts or economists may express professional opinions that fall short of definitive proof, so may scientists.

To be sure, some opinions of scientists must be excluded in the exercise of the district court's gatekeeping role. The objective "is to make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire,* 526 U.S. at 152. To be admissible, the opinion must be reasonably based on good science. The analogies,

inferences and extrapolations connecting the science to the witness's conclusions must be of a kind that a reasonable scientist or physician would make in a decision of importance arising in the exercise of his profession outside the context of litigation. If the court finds the gap too great between the science and the witness's conclusion, the opinion is inadmissible. *General Electric v. Joiner,* 522 U.S. at 146.

Often, however, "gaps or inconsistencies in the reasoning leading to [the] opinion ... go to the weight of the evidence, not to its admissibility." *Campbell v. Metropolitan Property and Casualty Ins. Co.*, 239 F.3d 179, 186 (2d Cir. 2001). "Disputes as to [a medical expert's] use of differential etiology as a methodology ... go to the weight, not the admissibility, of his testimony." *McCullock*, 61 F.3d at 1044; *accord, Zuchowicz*, 140 F.3d at 388. Thus, although "an expert's analysis [must] be reliable at every step," *Amorgianos*, 303 F.3d at 628, analogy, inference and extrapolation can be sufficiently reliable steps to warrant admissibility so long as the gaps between the steps are not too great.

From the evidence presented to the Court at the hearing on the instant motions, it is apparent that no scientific study has been conducted that "proves" that ephedra or ephedrine "causes" any of the listed injuries in the sense of establishing the high statistical relationship (discussed below) that meets accepted

scientific standards for inferring causality. Nor, for that matter, are there studies that definitively disprove the hypothesis of causality. One reason for the paucity of such studies is Congress' decision in the Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417, 108 Stat. 4325 (1994) (codified in scattered sections of 21 U.S.C.), to exempt the sale of "dietary supplements," including ephedra-containing products, from any requirement of prior approval by the Federal Drug Administration ("FDA") unless the supplement producers make claims about the effects of the product in controlling disease. *See Nutraceutical Corp. v. Crawford*, 364 F. Supp. 2d 1310, 1312 (D. Utah 2005). Furthermore, as discussed below, such studies are extremely expensive. Further still, such studies, when performed on human beings, are potentially dangerous, unless they are retrospective in nature (*i.e.*, after-the-fact), in which case they become even more difficult and expensive.

But the absence of definitive scientific studies establishing causation did not prevent the FDA from banning the sale of ephedra-containing products as too risky. *See* 21 C.F.R. § 119.1; FDA's Response to Comment 19, *Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk* (hereinafter "FDA Final

Rule"), 69 Fed. Reg. 6788, 6799 (February 11, 2004).[4] Nor should it deprive a jury of having before it scientific opinions that, while less definitive and more qualified than the statistically significant scientific studies called for by the DCC, nevertheless meet scientific standards for determining the plausibility of a causal relationship.

Daubert was designed to exclude "junk science." It was never intended to keep from the jury the kind of evidence scientists regularly rely on in forming opinions of causality simply because such evidence is not definitive. The legal standard, after all, is preponderance of the evidence, *i.e.*, more-probable-than-not, and that applies to causality as to any other element of a tort cause of action. Rule 702, a rule of threshold admissibility, should not be transformed into a rule for imposing a more exacting standard of causality than more-probable-than-not simply because scientific issues are involved. It is one thing to prohibit an expert witness from testifying

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[4]Prior to the FDA ban, products containing ephedra were very widely used. A random telephone survey of nearly 15,000 adults in five states showed that 1% of respondents -- extrapolated to 2.5 million people nationwide -- had used ephedra products for weight loss in 1996-98. Blanck HM, Khan LK, Serdula MK, *Use of nonprescription weight loss products: results from a multistate survey* (JAMA, 2001, 286:930), DCC Exh. A68. Another article used sales data from ephedra manufactures to estimate that 12 million people consumed ephedra products in 1999. Haller CA and Benowitz NL, *Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids*, (NEW ENGL J MED, 2000, 343:25, 1833-1838), DCC exh. A234 at 1838.

that causality has been established "to a reasonable degree of scientific certainty" when the very exacting standards for determining scientific certainty have not been met. But it by no means follows that a scientific expert may not testify to the scientific plausibility of a particular hypothesis of causality or even to the fact that a confluence of suggestive, though non-definitive, scientific studies make it more-probable-than-not that a particular substance (such as ephedra) contributed to a particular result (such as a seizure).

The difference between statistical significance and preponderance of the evidence is well illustrated by an examination of the one study that attempted to measure a possible association between ephedra and hemorrhagic stoke (one of the five listed injuries), namely, Morgenstern LB *et al.*, *Use of ephedra-containing products and risk for hemorrhagic stroke* (NEUROLOGY, 2003, 60:132-135), DCC Exh. A404 (hereinafter *Morgenstern*). *Morgenstern* found a fivefold increased risk of hemorrhagic stroke in participants who had taken more than 32 mg of ephedra alkaloids on the day before a stroke. The result, however, was not statistically significant because of the small number of participants found to have taken ephedra at this dose, even though a typical recommended dose of the products in the instant cases is 96 mg/day.

Morgenstern was a re-computation of data collected by Kernan

et al. in a study of the association between hemorrhagic stroke and products containing norephedrine (one of the ephedrine alkaloids found in ephedra products), which the Kernan study calls by its chemical name phenylpropanolamine or "PPA."[5] Synthetic PPA, like ephedra, had been widely marketed for weight loss. Also like ephedra, PPA had been the subject of published case studies and adverse event reports, sent spontaneously to the FDA and manufactures, reporting stokes suffered by users of PPA products. These reports led the *Kernan* investigators to "collaborate" with the FDA and PPA manufacturers to design and undertake the PPA study beginning in 1992. It took them until December 1994 to enroll the first case, until July 1999 to collect enough data, and until December 2000 to publish the results -- *i.e.,* more than eight years between the undertaking and the published article. *Kernan* at 1827.

In this case-control study, the "cases" were hemorrhagic-stroke patients whom the investigators enrolled into the study after they were admitted to one of 43 participating hospitals in six states. To be enrolled, patients, in addition to meeting certain medical criteria (diagnosis of hemorrhagic stroke and the absence of certain internal risk factors for stroke), had to agree and be able to answer questions within 30 days after their

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[5]Kernan WN et al., *Phenylpropanolamine and the risk of hemorrhagic stroke* (NEW ENG J MED 2000, 343:25, 1826-1832) ("Kernan"), DCC Exh. A302.

strokes about what medications and diet pills they had taken within two weeks before their strokes. As soon as a patient was enrolled, investigators searched by random telephoning for two matching "controls" -- two people with the same gender, age, and geography as the enrolled patient, who were willing to answer, within 30 days after the enrolled patient's stroke, the same questions about medications and diet pills taken within two weeks before the enrolled patient's stroke. After 4½ years, the investigators had gathered usable data from enough subjects to get statistically significant results for PPA -- 702 enrolled patients and 1,376 controls.

The questions asked by the PPA investigators were designed to gather information about all medications and diet pills without revealing that PPA was the subject of the study. *Kernan* at 1831. As a consequence, the PPA study gathered data on use of ephedra products along with the data on PPA. This, in turn, made it possible for *Morgenstern* subsequently to compute odds ratios for ephedra without gathering any new data.[6] The computation yielded (*inter alia*) an adjusted odds ratio for hemorrhagic

[6]It is possible that the PPA study undercounted ephedra use because some responding subjects might not have considered ephedra a medication or a diet pill. *Morgenstern* concludes, however, that such undercounting is equally likely for enrolled patients and controls, and that it therefore would not effect the computed odds ratios. Dr. Walter N. Kernan -- the lead author of *Kernan,* a co-author of *Morgenstern,* and an expert designated in this case by the DCC -- agrees. Kernan Report at 6.

stroke of 5.89 among participants who took more than 32 mg of ephedra within 24 hours before the cases' strokes. If this result were statistically significant, it presumably would satisfy the DCC's call for a scientifically valid study showing that ephedra increases the risk (by more than five times) of hemorrhagic stroke. But the DCC says the *Morgenstern* results cannot support opinion testimony on general causation because they fail to meet science's conventional test for statistical significance.

In motion papers and through argument and examination of experts at the hearings, the DCC repeatedly showed the Court how epidemiological studies quantify statistical significance in two ways -- the "P-value" and the "confidence interval." Generally accepted scientific convention treats a result as statistically significant if the P-value is not greater than .05. The expression "P=.05" means that there is one chance in twenty that a result showing increased risk was caused by a sampling error -- *i.e.*, that the randomly selected sample accidentally turned out to be so unrepresentative that it falsely indicates an elevated risk. "Confidence interval" measures the same risk of sampling error in a form that is less easy for a layman to picture. *Morgenstern* reports that the fivefold increased rate of hemorrhagic stroke among study participants who took more than 32 mg of ephedra on the day before the case's stroke has a "95% confidence

interval of 0.84 to 41.33." Because this interval includes the value 1.0 (which would mean no increased risk), the result is not considered statistically significant. This necessarily means that the P-value is greater than .05, though *Morgenstern* does not state the precise P-value.[7]

The reason why *Morgenstern*'s P-value is greater than .05 is that too few of the 702 stroke cases and 1,376 matching controls turned out to have taken more than 32 mg of ephedra within 24 hours before the case's stroke. In particular, only three controls had done so, even though the study design provided for two matching controls for each case. So the eight-year process described above, with 43 participating hospitals in six states, was insufficient to find enough ephedra users.

According to the DCC, plaintiffs should be required to do better. "I would design a much larger study," said Dr. Ebi, an epidemiologist designated by the DCC, in answer to questions from the Court. Tr. 1108 (Feb. 9, 2005). Instead of six exposed cases, Dr. Ebi said there should be 30 to 50, with a corresponding number of controls. *Id*. In other words, the DCC essentially argues that plaintiffs should be required to expend at least five times the effort spent by a group of PPA

[7]According to one of the PCC's experts, the P-value was .07. Tr. 240-41 (testimony of Dr. Franklin, Jan. 10, 2005). This would mean that the association found by *Morgenstern* between ephedra and hemorrhagic stroke has less than a one-in-14 chance of being due to a sampling error.

manufacturers prodded by the FDA's regulation of drug safety and labeling -- authority which Congress expressly withdrew from the FDA with respect to dietary supplements (including ephedra) in 1994.[8] Meanwhile, in answer to a question from the bench about how much a statistically significant study of ephedra and hemorrhagic stroke might cost, Dr. Ebi gave an off-the-cuff

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[8]It seems likely that a questionnaire designed to study ephedra might find a few more exposed subjects than the PPA questionnaire *without* greater effort -- subjects who used ephedra not as a "diet pill" but for increased energy or enhanced athletic performance, and who would not list the ephedra products they had used when asked about "medications." This small gain, however, would be far outweighed by the need for 30 to 50 cases and controls exposed to ephedra at a *dose* and for a *time period* relevant to the products in this case -- *e.g.*, 96 mg per day for up to 12 weeks. In *Morgenstern*, the number of controls found to have taken only 32 mg/day or less was *double* the number found to have taken more than 32 mg/day, so the effort required to find subjects exposed at 96 mg/day would be more than double. The duration of repeated exposure may also be significant in measuring risk. The FDA and the PCC's experts hypothesize that ephedra can cause injury in susceptible people by increasing their blood pressure and heart rate. Experts testified that an individual's blood pressure and heart rate normally vary over the course of a day, week and season, and that the effects of ephedra in an individual also vary over the course of the day in relation to when it was ingested and the individual's metabolism. If ephedra can sometimes be a contributing cause of heart attack, stroke, or sudden death in susceptible people, the injury might be triggered by the coincidence of peak events, such as transient peak blood pressure due to other causes occurring at the same time as peak ephedrine blood level. The longer the duration of repeated exposure, the more likely such coincidence will occur. A study designed to measure increased risk from the recommended use of ephedra products might need 30 to 50 controls who took 96 mg/day for 12 weeks. Given the eight-year effort in the PPA study that found just three controls with a single day's exposure of more than 32 mg, the task of producing statistically significant results measuring the risks associated with the recommended use of ephedra products is obviously beyond the capacity of any conceivable plaintiffs.

estimate of "a couple of million dollars." Tr. 1110. As for the cost of studying not only hemorrhagic stroke but also other risks of taking ephedra, an estimate reported by the FDA is that such a study would "require 4 to 8 years to complete and cost $2 million to $4 million per year." FDA Final Rule at 6846 (Response to Comment 97).

Thus, if the Court accepted the DCC's argument that plaintiffs must produce statistically significant results from a retrospective case-control study, the insurmountable practical obstacles would prevent injured parties from ever obtaining compensation even if such a study were theoretically possible. Here, moreover, a retrospective study is close to impossible even in theory because of the FDA's ban on ephedra as of February 2004. A retrospective study would require subjects to recall with precision when and in what amount they took ephedra. Because ephedrine is short-acting, in *Morgenstern* stroke patients were not considered exposed unless a known dose of ephedra was taken within 72 hours before their stroke. Mistaken memory by even a single day about how many pills were taken could make the data unreliable. So, to reduce errors of recall, the PPA study did not accept exposure data unless the questionnaire was answered within 30 days after the patient's stroke. For this reason, the FDA ban means it was no longer possible, after March 2004, to collect retrospective exposure data. Even on the

assumption that the "much larger study" demanded by the DCC could be done in the same time frame as the PPA study, for data collection to be completed by March 2004 the study would have had to be funded and initiated before 1998. Very few (if any) of the 500 cases pending in this Court allege injury before 1998. Thus, even if plaintiffs had somehow mobilized millions of dollars to undertake a study immediately after their injury, the FDA ban would have cut the study off before enough data could be collected to make the results statistically significant.

Scientific convention defines statistical significance as "$P \leq .05$," *i.e.*, no more than one chance in twenty of a finding a false association due to sampling error. Plaintiffs, however, need only prove that causation is more-probable-than-not.[9] Although this legal standard may lead to what some scientists might consider an unacceptably high error rate in jury verdicts, the law has tolerated the jury error rate for centuries because it has not yet found a better way of adjudicating disputes. This Court will be guided by *Daubert*'s "general observations" about scientific knowledge in its determination to keep junk science out of the courtroom. At the same time, it will not treat *Daubert*'s dictum about scientific validity as authority for

[9]More-probable-than-not might be likened to $P<.5$, so that preponderance of the evidence is nearly ten times less significant (whatever that might mean) than the scientific standard.

increasing the burden of proof imposed by substantive law.

Here, it was the PCC's job to designate a roster of experts on general causation so that at least one PCC expert would be available to testify at trial -- here or in other federal courts after remand pursuant to 28 U.S.C. § 1407 -- in any of nearly 500 cases. This necessarily meant that the same opinion based on the same data, principles, and methods would be offered by multiple experts, and that details of the DCC's Rule 702 challenge to that generic opinion would be repeated from expert to expert. Considering first, then, the issue of what generic opinion may be given by the PCC's generic experts, the Court concludes that the following generic opinion (or words to that effect) is sufficiently reliable to be admitted under Rule 702: "Ephedra products may be a contributing cause of stroke and cardiac injury in some people." As noted, however, this opinion must be accompanied by the qualifications that there is not enough scientific data to prove such a causal relationship definitively and that controlled studies, if and when they are done, may disprove it.

The PCC and DCC agree on part of the science underlying this opinion. They agree that a recommended dose of a product containing ephedra and caffeine often raises the user's blood pressure and/or heart rate during the first few hours after ingestion, and they agree that any increase maintained over *years*

in a person's usual blood pressure or heart rate significantly increases the risk of cardiac injury and stroke. The DCC argues, however, that there is no valid scientific basis for concluding that ephedra products taken as recommended for a few *months* increase the risk of cardiac injury and stroke.[10] In support of this argument, the DCC established at the hearings that the scientific literature is sparse and inconclusive on three points: (1) whether the cardiovascular effects of ephedra products persist beyond the first few doses; (2) whether the risk of stroke and cardiac injury is increased by transient increases in blood pressure and/or heart rate; and (3) whether the risk of stroke and cardiac injury is increased by a sustained increase in blood pressure and/or heart rate of less than six months.

The generic opinion overcomes these problems by inferences based on *Morgenstern*, published case studies, spontaneous adverse event reports ("AERs"), and biological plausibility discerned from animal and *in vitro* studies. The PCC experts cite published, peer-reviewed case studies describing patients who suffered heart attacks or strokes soon after exposure to ephedra or ephedrine, some of whom had no known risk factors that might

[10]The Metabolife 356 label does not state any maximum period for continuing the daily "suggested use" of up to 96 mg. The label of Metab-O-LITE (PCC Exh. 17), which was a competing product, states: "The maximum recommended dosage of ephedra alkaloids for a healthy adult human is no more than 100 mg in a 24-hour period for not more than 12 weeks."

otherwise explain the injury. They cite published analyses of AERs reporting heart attacks and strokes temporally associated with ephedra use that suggest (but do not prove) that ephedra can cause cardiac injury and stroke. They cite the biological mechanism -- generally accepted in medicine -- whereby ephedrine binds to alpha and beta-1 adrenergic receptors to stimulate cardiovascular activity and constrict blood vessels, thereby increasing stress on the heart and circulatory system, and from this they infer a biological pathway from ephedra products to heart injury and stroke. Finally, they cite the "outliers" and dropouts in published medical studies of ephedra products -- participants exposed to ephedra whom the investigators recorded as experiencing blood pressure or heart rate significantly higher than the mean, or who dropped out of the study because of adverse cardiovascular events, even though the screening for enrolment had admitted only subjects who tested normal for heart and blood pressure and had no known cardiovascular risk factors. From these outliers and dropouts who showed an unusually strong response to ephedra -- a small percentage of study participants, but enough to show up in studies involving fewer than 100 exposed subjects -- the PCC experts infer that some people are at significantly greater risk for cardiac injury and stroke than the average user of ephedra products.

The DCC says the gaps bridged by these inferences are too

great for the generic opinion to be admissible. The Court concludes, however, that the inferences are based on the kind of plausible and suggestive, even if inconclusive, scientific data generally relied upon by physicians and epidemiologists when they must make a decision of importance in the absence of conclusive proof. Although the gaps between such data and definitive evidence of causality are real and subject to challenge before the jury, they are not so great as to require the opinion to be excluded from evidence. Inconclusive science is not the same as junk science.

Specifically, in this case, the PCC's generic opinion, as recharacterized by the Court above, was formed with "the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire,* 526 U.S. at 152. Indeed, at least three of the PCC's experts expressed virtually the same opinion professionally before they were retained as litigation experts, at a time when ephedra lawsuits were rare or unknown. In 1996, Dr. Franklin published a warning in the scientific journal NEUROLOGY to "alert neurologists to the potential association of acute neurologic events with ingestion of dietary supplements containing *Ephedra* marketed for weight loss and energy purposes." Among the "acute events" were two cases of stroke. DCC Exh. A190. Also in 1996, Dr. Woosley published the results of his 1993-95 investigation of 88 cases in

Texas of suspected toxic reactions to ephedrine-containing products and concluded that they "constituted a real and serious health risk to anyone who may take them." Woolsey Report at 9-10 and n.4. In 1998, when Dr. Haller was a consultant for the California Poison Control System and fellow in medical toxicology at the University of California San Francisco, the University quoted her in a public warning about ephedra supplements: "Adverse effects related to products that contain ephedrine have included stroke, heart attack, seizures and even death." Tr. 143; DCC Exh. E-1011. A familiar form of junk science is the expert opinion expressed solely as a means to an end in litigation. Here, the record shows that the generic opinion was repeatedly expressed by experts in the field for professional purposes completely independent of litigation.

Further corroboration is found in the FDA Final Rule banning ephedra products. The DCC correctly points out that the *decision* of an agency to ban or limit a substance does not establish causation *per se*. An agency charged with health or safety might well ban a non-essential substance like ephedra simply because it is "better to be safe than sorry." *See* REF. MAN. SCIENTIFIC EVID., *supra*, at 33. The FDA Final Rule, however, is much more than the ban of ephedra codified at 21 C.F.R. § 119.1. The Final Rule fills 66 pages of the Federal Register, many of which are devoted to scientific issues directly relevant to the PCC's generic

opinion. Through the regulatory comment process, ephedra manufacturers and distributors made to the FDA many of the scientific arguments they have made here in the DCC's Rule 702 motion, and the FDA addressed those arguments, together with the underlying scientific studies and data, in its responses. The FDA, agreeing with comments that its rulemaking on ephedra had to be based on "sound science," explained:

> We have spent a great deal of time and effort compiling and evaluating the best available scientific evidence relevant to this rulemaking, and our decision is based on a careful, objective analysis of the most current information, including peer reviewed studies. In considering whether dietary supplements containing ephedrine alkaloids present an unreasonable risk, we considered evidence from three principal sources: (1) The well-known, scientifically established pharmacology of ephedrine alkaloids; (2) peer-reviewed scientific literature on the effects of ephedrine alkaloids; and (3) the adverse events (including published case reports) reported to have occurred following consumption of dietary supplements containing ephedrine alkaloids.

Final Rule at 6800 (Response to Comment 21). This "careful, objective analysis" led the FDA to the same conclusions as the PCC's generic opinion:

> People who use dietary supplements containing ephedrine alkaloids are at increased risk for serious adverse events, including heart attack, stroke, and death. Susceptible individuals (*e.g.*, those with coronary artery disease or heart failure), many of whom may not know they have underlying illnesses, are at increased risk for adverse events because these products can cause abnormal heart

> rhythms (pro-arrhythmic effect), even when the product is ingested at recommended doses over a short course (one or a few doses). Over longer periods of use, the risk for adverse health effects to the general population, including susceptible individuals, increases further due to a sustained elevation in blood pressure. This is a characteristic effect of the sympathomimetic class of pharmacological compounds. Moreover, the results of Boozer, *et al*. (2002) demonstrate that weight loss achieved with botanical ephedrine alkaloids does not produce the expected decrease in blood pressure [citation]. The risk of experiencing harmful effects from elevated blood pressure increases the longer the blood pressure remains high, and such adverse effects are likely to occur sooner in individuals with hypertension, many of whom are unaware of their illness.

Id. at 6825 (Response to Comment 63). Thus the FDA makes the same inferences from good but inconclusive science as the PCC's experts. This confirms that the inferences made to bridge gaps in the PCC's generic opinion are of the kind reasonably made by experts in the field when faced with a decision of importance.[11]

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[11]Recently, the District Court in Utah determined that the FDA improperly banned the sale of ephedra-containing products that have a dosage of 10 mg or less, because, on its reading, "there was not sufficient evidence in the administrative record to establish that the risks identified by the FDA are associated with the intake of low-dose [ephedra-containing products]." Accordingly, that Court enjoined the FDA from taking any enforcement action against the plaintiffs in that case for their sale of dietary supplements containing 10 mg or less of ephedrine alkaloids per daily dose. *Nutraceutical Corp.,* 364 F. Supp. 2d at 1321. Though instructive, *Nutraceutical* has no bearing on the questions of causation addressed in this case, because that court hinged its reasoning and conclusion on the FDA's failure to prove that ephedra-containing products present an unreasonable risk at "any dose, no matter how small," *id.* at 1320, while here the

Although the Court, therefore, concludes that the PCC's generic opinion, as modified above, certain qualifications are in order. The first refers to one aspect of cardiac injury, known as the "QT interval." One of the many studies cited by PCC experts in support of their generic opinion, a study by McBride *et al.*,[12] reported that a single dose of Metabolife 356 lengthened the mean corrected QT interval, measured by electrocardiogram, in a group of 15 young and health subjects. Several PCC experts testified that a lengthened QT interval can lead to a potentially fatal arrhythmia known as torsades de pointes. If valid, the *McBride* results would show an independent pathway for cardiac injury in addition to the cardiovascular stimulation and increased blood pressure on which the PCC's generic opinion is primarily based.

However, the PCC's own cardiologist, Dr. Zipes, testified that the *McBride* results were surprising because the well-documented effects of ephedrine would be expected to shorten rather than prolong the QT interval. Tr. 947 (Feb. 2, 2005). The DCC then called a cardiologist, Dr. Robert Myerburg, who had examined some of the electrocardiogram tracings underlying the

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Court's focus is on the reliability and admissibility of studies regarding ephedra-containing products of doses of more than 10 mg.

[12]McBride BF *et al.*, *Electrocardiographic and Hemodynamic Effects of a Multicomponent Dietary Supplement Containing Ephedra and Caffeine* (JAMA 291:2, 216-222, Jan. 14, 2004), DCC Exh. A375.

McBride study. Dr. Myerburg testified that he found flaws in *McBride*'s measurement of QT intervals in two of the 15 test subjects, and that these flaws were enough to invalidate the *McBride* results. Tr. 991. After this testimony, a member of the PCC, stating that the PCC, too, had "done an analysis" of the *McBride* tracings, requested and obtained the Court's permission to respond to Dr. Myerburg. Tr. 993. However, the PCC never availed itself of this opportunity.

On the record as it stands, the PCC has failed to meet its burden of showing the reliability of its experts' opinions regarding adverse effects of ephedra on the QT interval. That aspect of their opinion, therefore, is excluded under Rule 702. Since the QT results were cumulative and independent of the primary basis for the PCC's generic opinion, this ruling does not affect the admissibility of that opinion in general.

Turning to seizure, Dr. Franklin and Dr. Haller will be permitted to express at trial the opinion that "ephedra products may be a contributing cause of seizures in some people." As with the generic opinion described above, however, they must qualify this opinion by acknowledging that there is not enough data to prove it scientifically and that further studies might show that they are wrong.

Franklin and Haller base their opinion on (1) published case reports describing seizures temporally associated with ephedra

use in the absence of other risk factors; (2) an analysis by Dr. Haller and colleagues at the San Francisco Poison Control Center of 65 reports of seizure among users of herbal supplements, 19 of which, Dr. Haller and her colleagues concluded, were probably associated with ephedra; (3) many standard medical textbooks that list ephedrine along with other sympathomimetic drugs (such as amphetamine) as associated with seizures; (4) animal studies showing that ephedrine lowered the threshold for seizure, and also associating amphetamine with seizure; and (5) the biological plausibility of ephedra's causing seizures through its generally recognized capability of causing a sudden transient rise in blood pressure and of stimulating neurons in the brain. For reasons already set forth above, the Court finds that the gap between what these sources reasonably imply and more definitive scientific proof of causality is not too great to prevent the opinion from being admissible, because the inferences are of a kind that physicians and scientists reasonably make from good but inconclusive science when faced with practical decisions of importance.

It may be noted in this regard that the DCC, in its closing brief, makes an argument based on Dr. Franklin's testimony that confuses the Court's role under Rule 702 with the jury's role at trial. At the hearing, the DCC confronted Dr. Franklin with a number of animal studies tending to show that amphetamine may

have *anti*-convulsive effects (*i.e.*, that amphetamine might sometimes prevent rather than cause seizures). Dr. Franklin had not reviewed those articles, was taken by surprise, and under the pressure of cross-examination tried to discount them in part because they were animal studies of amphetamine rather than human studies of ephedra or ephedrine. This spontaneous testimony was inconsistent with Dr. Franklin's reliance in his report on animal studies and analogies to amphetamine. The DCC argues that these responses on cross-examination show that Dr. Franklin's opinion is inadmissible under Rule 702 because a method underlying his opinion -- consulting the medical literature -- was incomplete, biased, inconsistent, and, therefore, unreliable.

Clearly, the DCC's cross-examination of Dr. Franklin might properly lead a jury to doubt his credibility and accept instead the opinion of the DCC's expert, Dr. John Olney (who also testified at the hearing), that there is no scientific basis for concluding that ephedra causes seizures. But the Court's role is not to weigh Dr. Franklin's credibility but to determine if his opinion has a sufficiently reliable basis to be admissible at trial. The opinion that "ephedra products may be a contributing cause of seizure in some people" has a sufficiently reliable basis in the analyzed cases associating ephedra with seizures and, especially, in the many medical textbooks that report ephedrine's potentially convulsive properties. Medical textbooks

reflect the scientific consensus that has passed through a "knowledge filter" and survived the "test of time [that] is the ultimate test of data and theories." *See* K. Foster & P. Huber, JUDGING SCIENCE: SCIENTIFIC KNOWLEDGE AND THE FEDERAL COURTS (MIT Press, 1999) at 159-62. Although textbooks doubtless contain some statements that later will be proven wrong, the listing of ephedrine in many textbooks as associated with seizures evidences "widespread acceptance" in the medical community -- a key factor for admissibility under Rule 702. *Daubert*, 509 U.S. at 594. While "general acceptance" in the scientific community is no longer *necessary* for admissibility, it is frequently sufficient.

Turning finally to heat injury, the PCC proffered but one expert on this issue, namely James Knochel, M.D. However, the DCC's examination of Dr. Knochel at the hearing established that his opinion that ephedra can impair heat dissipation lacks a sufficiently reliable basis, as does his use of data regarding cocaine in making inferences about ephedra. Such testimony is therefore excluded. Those parts of Dr. Knochel's report that describe -- without reference to ephedra or ephedrine -- the normal physiology of heat regulation and the disease process and treatment of heat-related illness are sufficiently reliable to be admissible, as is his testimony that ephedra increases metabolism and thus causes a modest increase in the heat generated by the body.

At the hearing, the Court permitted Dr. Knochel to testify on one topic not included in his report: an observed surge of norepinephrine in patients suffering heat stroke. According to the PCC's experts, ephedrine acts in the body like norepinephrine (one of the body's neurotransmitters) and also causes cells to release norepinephrine -- points which the DCC does not dispute. Because the DCC had not had an opportunity to depose Dr. Knochel about this clinical observation, the Court, in allowing the testimony, said it would consider an application to call Dr. Knochel back for further examination by the DCC, Tr. 512 (Jan. 12, 2005); but in the end the DCC did not request further testimony. Accordingly, Dr. Knochel's clinical observations about a surge of norepinephrine in patients suffering heat stroke is deemed sufficiently reliable to be admissible, along with testimony about ephedrine's generally recognized property of acting like, and causing the release of, norepinephrine in the body. Also sufficiently reliable -- so long as he qualifies it by acknowledging that there is not enough data to prove it by scientific standards -- is Dr. Knochel's professional opinion that ephedra use coinciding with factors that put the user at risk for heat stroke (*e.g.*, strenuous exercise in hot weather) probably increases the risk of heat stroke.

Turning to the PCC's motion to exclude the testimony of just one of the DCC's experts, namely, Kristie L. Ebi, M.D., Dr. Ebi

summarized his opinion as follows: “I have determined that there is no valid scientific evidence from which to conclude, using generally accepted scientific methods, that ephedra or ephedrine causes stroke, seizure, acute myocardial infarction, or sudden cardiac death.” Ebi Report, ¶ 14; *id.,* ¶ 97. This opinion can be made reliable under Rule 702 by twice replacing the word “scientific” with the word “epidemiological.” Dr. Ebi is an epidemiologist and does not purport to have training and experience in medicine. Epidemiology uses statistical methods to quantify risk in populations and has generally accepted standards of statistical significance. The pending motions have established that there is only one published epidemiological study of the relative risk of a listed injury in people exposed to ephedra -- the *Morgenstern* study of hemorrhagic stroke, whose results failed to meet the generally accepted standard of a 95% confidence interval above 1.0. Therefore, Dr. Ebi’s opinion that there is no valid epidemiological evidence for concluding that ephedra causes any of the listed injuries is reliable under Rule 702. In contrast, the opinions of the PCC’s experts held in this decision to be sufficiently reliable are not based on epidemiology but on the kind of inferences from good but inconclusive science that physicians reasonably make, drawing on their medical knowledge, training and experience. A jury might interpret the word “scientific” in the summary of Dr. Ebi’s opinion quoted

above as contradicting medical inferences reasonably relied upon by the PCC's experts. The chance of such confusion will be reduced by changing "scientific" to "epidemiological."

To implement the determinations reached in this Opinion and Order, the Court directs the PCC, within thirty days of the date of entry of this Opinion and Order, to serve on the DCC revised reports omitting the facts and data held insufficiently reliable and revising the experts' summaries and conclusions to conform to this Opinion and Order. The DCC shall do the same with Dr. Ebi's report. Within ten days after service, respective coordinating counsel for both the PCC and PCC may, if they wish, apply for a ruling by the Special Master that any given revised report does not conform to this Opinion and Order, in which case the Special Master may require further revisions. Each expert's direct testimony at trial shall be limited to the content of such revised report approved by the Court.

Lastly, the PCC's motion to have the DCC pay the fees of the PCC's experts for their attendance at the Rule 702 hearings is hereby denied.

SO ORDERED.

JED S. RAKOFF, U.S.D.J.

Dated: New York, New York
September 19, 2005